REMARKS

The invention provides methods for immunizing against Helicobacter infection, which include (i) mucosal administration, followed by parenteral administration, and/or (ii) subdiaphragmatic administration. As is discussed further below, these methods can be used with any of a large number of known Helicobacter antigens, many of which were known to be prophylactically and/or therapeutically effective at the time applicants' earliest priority application was filed. The methods of the present invention are advantageous because, as is shown throughout the application, they are more effective than what was previously considered to be the most efficacious Helicobacter vaccination regimen, involving strict mucosal administration. An additional advantage of the present methods is that they include parenteral administration, which requires less antigen per administration than mucosal administration.

Examination of claims 1-18 and 25 is reported in the present Office Action. Claim 25 was rejected under 35 U.S.C. §§ 112, first paragraph and 103(a); claims 1-4, 6-9, and 25 were rejected under 35 U.S.C. § 112, second paragraph; and claims 1-18 were rejected under 35 U.S.C. §§ 101, 102(b), and 102(e). Each of the rejections is addressed below.

First, applicants note that the specification was objected to for including brackets at page 20, lines 25-27; page 21, lines 1, 2, and 25-27; and page 22, lines 4-8. This objection has been met by the present amendment, in which the brackets in these passages have been removed.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 25 was rejected under § 112, first paragraph for lack of enablement. The Examiner states that, while the specification enables the induction of an immune response, it does not

provide enablement for the administration of any immunogenic agent in a method for preventing or treating Helicobacter infection. This rejection is respectfully traversed.

In response to the Examiner's concerns that the antigen used in the method of claim 25 can be any Helicobacter antigen, administered in any amount, to induce any type of immune response (page 4, lines 3-12 of the Office Action), applicants note that claim 25 has now been amended to specify administration of a prophylactically or therapeutically effective *Helicobacter pylori* antigen. (Applicants reserve the right, however, to pursue the original or similar claims in future applications.) Thus, rather than covering the use of any immunogenic agent derived from Helicobacter, claim 25 now requires that the immunogenic agent be a prophylactically or therapeutically effective *Helicobacter pylori* antigen. As is discussed further below, numerous examples of such antigens were known in the art at applicants' earliest priority date, and it would not have required undue experimentation to use these or other antigens in applicants' method.

Claim 25 has also been amended to specify that an effective amount of the antigen is used in the claimed method. Determination of what constitutes an effective amount of a vaccine antigen for a particular subject, such as a human, is a standard practice for medical professionals and can be carried out in the absence of undue experimentation. Indeed, the experiments described in the present application may provide particularly useful guidance for this determination, as some of these experiments were carried out in non-human primates (see, *e.g.*, pages 29-33 and 35-37 of the specification). Applicants also note that claim 25 specifies that the claimed method is for preventing or treating Helicobacter infection, thus making it clear that it is a prophylactic or therapeutic immune response that is induced using the claimed method.

As is mentioned above, numerous examples of effective *H. pylori* antigens were known in the art at the time of applicants' priority date, and any of these could have been used in the

method of claim 25. For example, several of these antigens are listed at page 11, lines 13-19 and 24-26 of the specification. Papers and patent publications showing the efficacy of several examples of these and other *H. pylori* antigens in vaccination methods are enclosed, and these antigens include urease (Michetti *et al.*, Gastroenterology 107:1002-1011, 1994 (Exhibit A); Corthésy-Theulaz *et al.*, Gastroenterology 109:115-121, 1995 (Exhibit B); Cuenca *et al.*, Gastroenterology 110:1770-1775, 1996 (Exhibit C)); HspA and HspB (Ferrero *et al.*, Proc. Natl. Acad. Sci. U.S.A. 92:6499-6503, 1995 (Exhibit D)); vacuolating cytotoxin (VacA; Marchetti *et al.*, Science 267:1655-1658, 1995 (Exhibit E)); catalase (Radcliff *et al.*, Infection and Immunity 65(11):4668-4674, 1997 (Exhibit F); WO 95/33482, published December 14, 1995 (Exhibit G)); a 29 kDa lipoprotein (WO 96/38475, published December 5, 1996 (Exhibit H)); and antigens 447, 658, 812, 820, 865, and 880 (WO 96/40893, published December 19, 1996 (Exhibit I)). Any of these *H. pylori* antigens, which had proven vaccine efficacy, could have been used in the present invention. Indeed, as is stated in the accompanying Declaration under 37 C.F.R. § 1.132, several of these *H. pylori* antigens and others have been shown to be effective when used in a mucosal prime, parenteral boost regimen.

Moreover, if one skilled in this art had wanted to use a different antigen in the claimed method, standard challenge models were available in the art (see, *e.g.*, pages 23-37 of the specification) and could have been used to determine whether a particular antigen could be used in the method. This level of experimentation certainly cannot be considered to be undue. Indeed, the leading Federal Circuit decision applying the undue experimentation standard in the field of biotechnology, *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), supports applicants' position on this point. The enablement issue in *Wands* related to whether the amount of experimentation required to obtain hybridomas that produced an antibody for use in a claimed

immunoassay was undue, and thus negated enablement. In reversing the Examiner's decision on this issue, the Court noted that the amount of experimentation is not necessarily decisive in a determination of enablement, if the type of experimentation is merely routine or if the specification provides guidance as to how the experimentation should proceed. Indeed, the Court noted that even if only 2.8% of hybridomas screened were found to produce a useful antibody, the enablement requirement would still have been met, because the methods used to screen them were routine, and the level of skill in the relevant art was high.

The same is true in the present case: routine challenge models were available, as well as described in the specification, and their use was routine. Moreover, the level of skill in this art is quite high, with many researchers holding advanced scientific or medical degrees. Further, the number of possible hybridomas *in Wands* could be considered to be infinite, while the number of possible antigens for use in the present methods is far more limited, especially in light of the present amendment, specifying that the antigens are *H. pylori* antigens. Thus, it is applicants' position that it would not have required undue experimentation to carry out the claimed method, using any of the numerous known effective *H. pylori* antigens, and that also it would not have required undue experimentation to identify other *H. pylori* antigens for use in this method.

The Examiner also states in this rejection that data from challenge experiments showing improvement are required for a skilled artisan to carry out the claimed methods (page 4, line 13 through page 5, line 2 of the Office Action), and further states that examples from an *in vitro* or *in vivo* model which show how a single immunogenic agent can result in prevention of infection or disease are not provided (page 6, lines 19-22 of the Office Action). In response, applicants note that the specification includes data from two art-accepted models of Helicobacter infection, the mouse and the monkey, using urease as an antigen. In addition, as is noted above, numerous

other *H. pylori* antigens were known to be effective at applicants' priority date, and several of these and other Helicobacter antigens have been shown to be effective in a mucosal prime, parenteral boost immunization regimen (see the enclosed Declaration under 37 C.F.R. § 1.132).

The Examiner further states in this rejection that patients that are infected with Helicobacter produce an immune response that can be detected diagnostically, but which is not therapeutic, as infection persists in these patients. However, it has been shown repeatedly that, in spite of this observation, vaccine efficacy can be achieved (see, *e.g.*, the references mentioned above).

The Examiner also cites several references in support of this rejection, which, according to the Examiner, show that Helicobacter vaccination is unpredictable. For example, the Examiner refers to several passages from HP-Worldwide, including a statement that "immunization does not appear promising." HP-Worldwide was published in 1992, while the priority date of the present application is five years later, in 1997. Regardless of what the HP-Worldwide reference taught in 1992, it is not relevant to the state of the Helicobacter vaccine art in 1997. Indeed, during the time period between the publication of HP-Worldwide and applicants' 1997 priority date, many developments took place in the field of Helicobacter vaccination that make the teachings of HP-Worldwide, with respect to whether vaccination is a feasible approach to the prevention and treatment of Helicobacter infection, essentially obsolete. During this time, as is shown, for example, in the references cited above, numerous Helicobacter antigens were shown to have efficacy in vaccination methods.

Citing the Boslego reference, the Examiner notes that the vaccine art includes many examples of well-characterized agents that induce neutralizing antibodies, as determined by *in vitro* assays, but fail to elicit *in vivo* protective immunity, and that the observation that an agent is

immunogenic does not mean that the agent can be used to treat or prevent infection (page 5, line 21 through page 6, line 6 of the Office Action). This should not be of concern in the present case because, as is noted above, claim 25 has been amended to require that the antigen used in the claimed method have prophylactic or therapeutic efficacy. As is discussed above, at the time of applicants' priority date, there were many *H. pylori* antigens that had been proven to have such efficacy, and any of these could have been used in the claimed invention. Moreover, as is stated in the accompanying Declaration under 37 C.F.R. § 1.132, efficacy of these and other antigens in the claimed method has been demonstrated. Thus, undue experimentation would not have been required to formulate and use a successful immunogenic agent in the claimed methods.

The Examiner also cites a 1993 reference by Rappuoli *et al.* as teaching four steps involved in the development of a vaccine against Helicobacter. As is discussed above, by the time of the priority date of the present application, several Helicobacter vaccine candidates had been developed, thus eliminating any concerns based on the Rappuoli reference.

The rejection under § 112, first paragraph should therefore be withdrawn.

Rejections under 35 U.S.C. §§ 112, second paragraph and 101

Claims 1-4, 6-9, and 25 were rejected under § 112, second paragraph for indefiniteness on several grounds, which are addressed as follows.

Citing the Campbell reference, the Examiner states that polyclonal antibodies in a host are not predictably produced to the same level in animals or between animals, and that claims 1-4, 6-9, and 25 do not specify what the immunogenic agent is. The Examiner further states: "the immunogenic agent is not distinctly claimed because the claim limitations recited are apparently contradictory (see page 5, lines 8-13; page 3, lines 6-8)." Applicants respectfully disagree.

As is set forth above, claims 1-4 have been canceled, and claims 5-18 have been amended to specify a method of inducing a protective or therapeutic immune response against Helicobacter in a mammal, involving subdiaphragmatic, systemic administration of a prophylactically or therapeutically effective Helicobacter antigen to the mammal. There is nothing in the Campbell reference that indicates that the use of such a method would lead to the production of unpredictable amounts of polyclonal antibodies.

The claims also now specify that the Helicobacter antigen is one that is prophylactically or therapeutically effective, which should address the Examiner's concern that the original claims did not specify what the immunogenic agent is. As is discussed above, numerous prophylactically and therapeutically effective Helicobacter antigens were known in the art at the time of applicants' priority date, and several of these antigens are listed in the specification at, *e.g.*, page 11, lines 13-19 and 24-26.

Finally, applicants note that the passage referred to by the Examiner on page 3 states that mouse Th1 cells can stimulate an antibody response, and, in particular, that IFN-γ, which is produced by Th1 cells, induces an IgG2a response. The passage on page 5 states that a useful Th1 response is characterized by increasing ratios of IgG2a:IgG1, ranging from 1/100 to 10 (*i.e.*, 10/1). It is unclear to applicants what the Examiner could consider to be inconsistent between these passages. The first states that Th1 cells, by way of IFN-γ production, lead to the production of IgG2a antibodies, and the second presents ranges of amounts of IgG2a antibodies, relative to IgG1 antibodies, which are characteristic of a Th2 response, that are indicative of a useful Th1 response. Applicants thus request that this rejection be withdrawn.

The Examiner further states that the recitation of ratios in which the IgG1 titer is greater than the IgG2a titer is confusing, because the base claim defines the intended immune response

to be predominantly Th1 (which is characterized by IgG2a antibodies), relative to Th2 (characterized by IgG1 antibodies). Claim 6, which is the relevant base claim, specifies that a Th1-type immune response is induced, but does not require that the Th1 response be predominant. Thus, the dependent claims (claims 7-9), which specify ratios in which IgG1 antibodies can be predominant, are consistent with the base claim.

Claims 1-18 were rejected under §§ 112, second paragraph and 101 for reciting a use, without setting forth any steps involved in the process of carrying out the use. This rejection can now be withdrawn, as claims 1-4 have been canceled, and claims 5-18 have been amended to specify methods, which each include at least one step.

Rejections under 35 U.S.C. §§ 102(b) and 102(e)

Claims 1-18 were rejected under § 102(b) as being anticipated by Guy *et al.* (WO 96/31235), in light of Guy *et al.* (U.S. Patent No. 6,126,938); Mohammadi *et al.* (J. Immunol. 156:4729-4738, 1996), Pappo *et al.* (Infection and Immunity 63(4):1246-1252, 1995), or Telford *et al.* (Drugs 52(6):799-804, 1996), and under § 102(e) as being anticipated by Morrow *et al.* (U.S. Patent No.5,817,512), Holmgren *et al.* (U.S. Patent No. 6,153,203), or Marciani (U.S. Patent No. 6,080,725). These rejections should be withdrawn.

As is noted above, claims 1-4 have been canceled, and claim 5, from which claims 6-18 depend, has been amended to be drawn to a method of inducing a protective or therapeutic immune response against Helicobacter in a subject by administration of a Helicobacter antigen using the subdiaphragmatic, systemic route. None of the cited references mentions immunization by use of a subdiaphragmatic, systemic route, as is required by amended claims 5-18. These rejections should therefore be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claim 25 was rejected under § 103(a) for obviousness over Guy *et al.*, WO 96/31235, which is in the French language, in light of Guy *et al.*, U.S. Patent No. 6,126,938, the English language specification of which corresponds to that of WO 96/31235. This rejection is respectfully traversed.

The Examiner refers to a passage at column 3, lines 32-40 of the '938 patent as describing the efficacy of an immunization regimen involving the use of mucosal (oral) followed by parenteral (subcutaneous) routes, and states that it would have been obvious to use a Helicobacter antigen in such a regimen, because Guy shows that immunization using a combination of mucosal and parenteral routes is effective in inducing an effective immune response against Helicobacter. Applicants disagree.

In particular, the passage referred to by the Examiner at column 3, lines 32-40 is a description of a prior art reference, Forrest *et al.*, Infection and Immunity 60(2):465, 1992 (a copy is enclosed as Exhibit J), which describes characterization of immunization regimens against *Salmonella typhi*, not Helicobacter, as is required by claim 25. One of these methods involved oral administration of a *S. typhi* antigen, followed by subcutaneous administration of such an antigen, and this method resulted in the induction of an intestinal IgA immune response.

It would not have been obvious to use Forrest's *S. typhi* immunization method to immunize against Helicobacter using a mucosal/parenteral approach for several reasons. First, applicants note that the study of Forrest only provides information as to the induction of an antibody response, and does not show that their oral/subcutaneous immunization method is prophylactically or therapeutically effective against even Salmonella, let alone indicate that it would be effective against any other type of pathogen. Moreover, even if Forrest had shown such

efficacy, which they did not, Salmonella and Helicobacter are different bacteria, and it may not necessarily be predictable that approaches used to immunize against one of these bacteria would be applicable to the other. For example, these bacteria differ in that Salmonella infects the intestine, while Helicobacter infects a different organ in the body, the stomach. Thus, the Forrest paper, as cited in the Guy publication, does not provide any teaching or motivation to use a mucosal/parenteral immunization method for vaccinating against Helicobacter.

Such motivation also does not come from elsewhere in the Guy reference, taken with or without the teachings of Forrest. Guy does not specifically suggest a Helicobacter vaccination regimen involving a mucosal prime, followed by a parenteral boost. In fact, Guy teaches away from such a method, as the focus of Guy is a regimen involving nasobuccal administration followed by administration by a second, non-nasal route (see, *e.g.*, column 4, lines 1-16). When systemic administration is added to this regimen, it is preferably carried out before the mucosal administrations (see, *e.g.*, column 4, lines 17-24). Thus, because the cited reference, Guy, teaches away from an immunization method requiring mucosal administration, followed by parenteral administration, as is specified by claim 25, this rejection should be withdrawn.

CONCLUSION

Enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including August 28, 2001, and payment of the corresponding extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: August 28, 2001

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The paragraph beginning at page 20, line 20 has been amended as follows.

Figure 1 refers to Example 1 and presents a study of the local response in the salivary glands (Figure 1A) and in the stomach (Figure 1B) evaluated by ELISPOT by measuring the quantity of anti-urease IgA induced, expressed as spots/10^6 cells (Figure 1A) or as number of responding mice, exhibiting more than 2 IgA spots/mouse, (Figure 1B), after (a) administration of urease at D0 by the subcutaneous route (SC) in the left posterior sublumbar part ([[](a) and (c)[]]) or in the neck ([[](b) and (d)[]]), followed by a booster by the nasal route (N) and intragastric route (IG), at D28 ([[](a) and (b)[]]) or at D28 and D56 ([[](c) and (d)[]]).

The paragraph beginning at page 20, line 28 has been amended as follows.

Figure 2 refers to Example 1 and presents the levels of urease activity after a challenge, measured 4 hours after sacrificing mice which have received 3 times, on D0, D28, and D56, an inactivated bacterial preparation by the intragastric route ([[](a) and (c)[]]) or subcutaneous route in the left posterior sublumbar part (b). In experiment (c), 10 μg of cholera toxin were added to the bacterial preparation. Experiments (d) and (e) correspond respectively to the positive and negative controls.

The paragraph beginning at page 21, line 18 has been amended as follows.

Figure 5 presents the quantities of serum immunoglobulins induced in monkeys subjected to the immunization procedures described in Example 2, and expressed as ELISA titre. A control group comprising 4 monkeys and three test groups are formed, each of the test groups comprising 8 monkeys; each test group is divided into two subgroups of 4 monkeys, one

receiving only the inactivated *H. pylori* preparation (1, 2, and 3) and the other receiving the inactivated *H. pylori* preparation and recombinant urease (1u, 2u, and 3u). Group 1 and 1u correspond [corresponds] to the administration procedure: [[]nasal + intragastric, 4 times[]]; group 2 and 2u correspond [corresponds] to the administration procedure: [[]intramuscular, 4 times[]]; group 3[1] and 3[1]u correspond [corresponds] to the administration procedure: [[]nasal + intragastric, intramuscular, nasal + intragastric, intramuscular[]]. The ELISA titre is measured three times: a first time at D0 (white band), a second time at D42 (shaded band), a third time at D78 (black band).

The paragraph beginning at page 22, line 2 has been amended as follows.

Figures 6A and 6B show the urease activity (Figure 6A) measured after 4 hours (OD_{550} nm) using the Jatrox test (Procter & Gamble) and the bacterial load in mice infected with *H. pylori* and then submitted to various treatments A-H ([[]A: LT + urease, orally; B: QS-21 + urease, parenterally in the neck; C: QS-21 + urease, parenterally in the lumbar region; D: QS-21 alone, sub-cutaneously in the lumbar region; E: Bay R1005 + urease, parenterally in the neck; F: Bay R1005 + urease, parenterally in the lumbar region; G: Bay R1005 alone, sub-cutaneously in the lumbar region (control); H: saline, sub-cutaneously in the lumbar region (positive control)[]]). I represents the negative control.

Claims 1-4 and 13 have been canceled, and claims 5-18 and 25 have been amended as follows.

5. (Amended) A method of inducing a protective or therapeutic immune response against Helicobacter in a mammal, said method comprising administering to said mammal an effective amount of a prophylactically or therapeutically effective [Use of an immunogenic agent derived

from] Helicobacter pylori antigen [, in the manufacture of a pharmaceutical composition intended to be administered] by the subdiaphragmatic, systemic route[, in the part of a mammal, especially the primate, situated under its diaphragm, to treat or prevent a Helicobacter infection].

6. (Amended) The method of [Use according to] Claim 5, in which [the composition is capable of inducing] a Th1-type immune response [when it] is induced [administered] by said [the] subdiaphragmatic, systemic administration [route].

7. (Twice Amended) The method of [Use according to] Claim 6 [5], in which the Th1-type immune response is characterized either (i) by a ratio of the ELISA IgG2a:[ ]IgG1 titers greater than or equal to 1:100, or (ii) by a ratio of the ELISA IgG2a:IgA titers greater than or equal to 1:100.

8. (Amended) The method of [Use according to] Claim 7, in which the Th1-type immune response is characterized either (i) by a ratio of the ELISA IgG2a:IgG1 titers [in mice] greater than or equal to 1:10, or (ii) by a ratio of the ELISA IgG2a:IgA titers [in mice] greater than or equal to 1:10.

9. (Amended) The method of [Use according to] Claim 8, in which the Th1-type immune response is characterized either (i) by a ratio of the ELISA IgG2a:IgG1 titers [in mice] greater than or equal to 1:2, or (ii) by a ratio of the ELISA IgG2a:IgA titers [in mice] greater than or equal to 1:2.

10. (Twice Amended) The method of [Use according to] Claim 5 [1], in which the [immunogenic agent derived from] Helicobacter pylori antigen is selected from a preparation of inactivated Helicobacter pylori bacteria, a Helicobacter pylori cell lysate, a peptide or a polypeptide from Helicobacter pylori in purified form, a DNA molecule comprising a sequence encoding a peptide or a polypeptide from Helicobacter pylori placed under the control of the elements necessary for its expression, and a vaccinal vector comprising a sequence encoding a peptide or a polypeptide from Helicobacter pylori placed under the control of the elements necessary for its expression.

11. (Amended) The method of [Use according to] Claim 10, in which the [immunogenic agent derived from] Helicobacter pylori antigen comprises [is] the UreB or UreA subunit of a [the] Helicobacter pylori urease.

12. (Amended) The method of [Use according to] Claim 10, in which the [immunogenic agent derived from] Helicobacter pylori antigen is a DNA molecule or a vaccinal vector comprising a sequence encoding the UreB or UreA subunit of a [the] Helicobacter pylori urease.

14. (Amended) The method of [Use according to] Claim 5, in which the [immunogenic agent pharmaceutical composition] Helicobacter pylori antigen is [intended to be] administered by the strict systemic route.

15. (Amended) The method of [Use according to] Claim 5, in which the Helicobacter pylori antigen [pharmaceutical composition] is [intended to be] administered by a systemic route selected from the subcutaneous route, the intramuscular route, and the intradermal route.

16. (Amended) The method of [Use according to] Claim 5, in which the Helicobacter pylori antigen [pharmaceutical composition] is [intended to be] administered by a mucosal route followed by a parenteral route.

17. (Amended) The method of [Use according to] Claim 16, in which the Helicobacter pylori antigen [pharmaceutical composition] is [intended to be] administered by a parenteral route, followed by a mucosal route, followed by a parenteral route, followed by a mucosal route.

18. (Amended) The method of [Use according to] Claim 5, in which the Helicobacter pylori antigen [pharmaceutical composition] is [intended to be] administered in the dorsolumbar region of [the] said mammal.

25. (Amended) A method of preventing or treating Helicobacter infection in a mammal, said method comprising in order the steps of:

mucosally administering an effective amount of a prophylactically or therapeutically effective [an immunogenic agent derived from] *Helicobacter pylori* antigen to said mammal; and then

parenterally administering [said immunogenic agent derived from] a *Helicobacter pylori* antigen to said mammal.